

Chemistry 17: Section Handout 3

Topics: Thermodynamics and kinetics; energy diagrams; transition state theory; reversibility and irreversibility; addition of nucleophiles to aldehydes and ketones; strong and weak nucleophiles

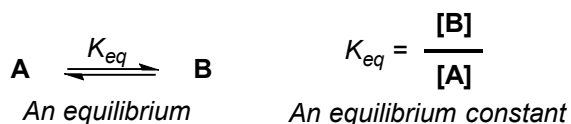
Key Concept Review

Reaction Energetics:

Gibbs free energy or "free energy": ΔG $\Delta G = \Delta H - T\Delta S$

$\Delta G < 0$ when a reaction is thermodynamically favorable (possible in the forward direction). This can be due to forming more stable bonds/ species (enthalpic factors), or by increasing disorder (entropic factors). Compounds can become more stable either through sterics (relieving strain), or electronics (charges placed on atoms that can better stabilize them, etc)

Equilibrium constant (K_{eq}): the relative concentrations of starting materials and products at equilibrium.



The change in free energy for a reaction can also be described in terms of the temperature and equilibrium constant.

- If the forward reaction is favorable: $\Delta G < 0$ and $K_{eq} > 1$
- If the reverse reaction is favorable: $\Delta G > 0$ and $K_{eq} < 1$
- If the forward and reverse reactions are equally favorable: $\Delta G = 0$ and $K_{eq} = 1$

gas constant:
 $0.00199 \text{ kcal K}^{-1} \text{ mol}^{-1}$

free energy $\Delta G = -RT \ln K_{eq}$ temperature

or

$$K_{eq} = e^{-\Delta G/RT}$$

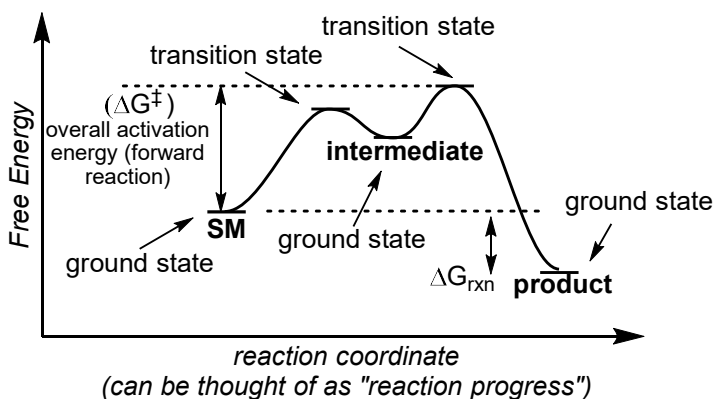
Free energy diagram or reaction energy profile diagram: a representation of the relative free energies of species (starting materials, intermediates, products, and transition states) in a reaction.

Key features of a free energy diagram include:

(1) **Ground state:** *relative energy minima* on a free energy diagram; includes all starting materials, intermediates, and products

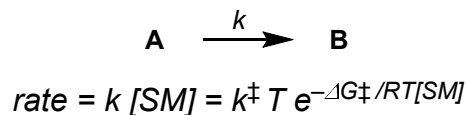
(2) **Transition state:** *relative energy maxima* on a free energy diagram; a single transition state connects each pair of ground states

(3) **Activation energy (ΔG^\ddagger):** the difference in energy between a ground state and transition state; the amount of energy needed for a step to occur. The overall activation energy is the amount of energy needed for the reaction to occur.



Transition state theory: The rate of a reaction is proportional to the concentrations of the reactants that come together in the transition state. The rate constant "**k**" (**this is a lowercase k**) is directly related to the activation energy of a process, and it will be characteristic of a particular reaction mechanism.

The larger the rate constant, the faster the reaction. For a reaction to take place at a measurable rate at room temperature (ca 300 K), it must have an activation barrier of $\Delta G^\ddagger < 25 \text{ kcal/mol}$.



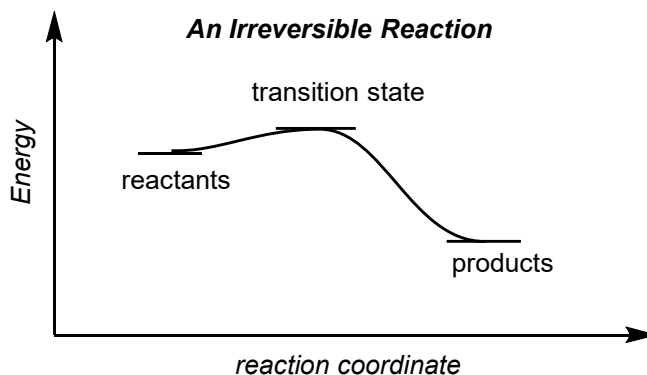
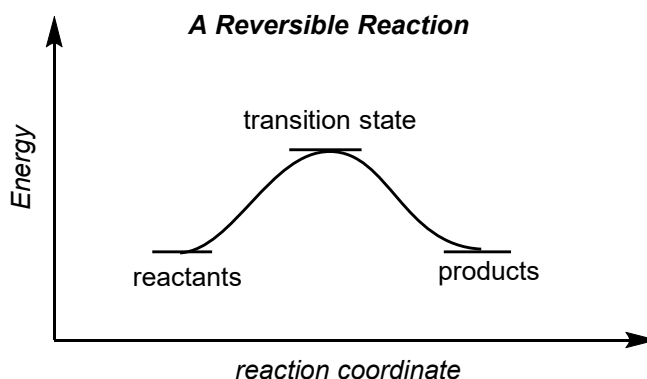
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The principle of microscopic reversibility: For every chemical reaction, the lowest energy reaction mechanism in the reverse direction must be the exact reverse of the lowest energy reaction mechanism in the forward direction.

Reversible reaction: A reaction where the forward and reverse reactions can both occur to a significant extent under the same conditions. This results in an equilibrium between reactants and products. This situation occurs when the reactants and products have free energies that are not too different (rule of thumb: $\Delta G < 13$ kcal/mol).

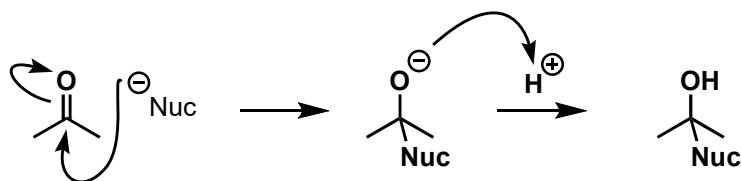
Irreversible reaction: In principle every reaction is reversible to some degree, but we call a reaction "irreversible" when the reverse reaction will not occur to any significant degree. There are two ways that a reaction can be effectively irreversible:

- (1) One or more products are removed from the reaction mixture as they are formed, e.g. gas evolution
- (2) The products are much more stable than the starting materials, such that the rate of the reverse reaction is prohibitively slow



Carbonyl Compounds as Simple Electrophiles:

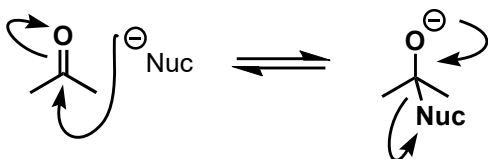
Irreversible addition to aldehydes and ketones: Reactions that involve the addition of strong nucleophiles to the $\pi^*_{C=O}$ to form products that are much more stable than the starting materials.



Strong nucleophiles: Reagents in which substantial partial negative charge is localized on atoms that are not very electronegative (especially C or H)

- Hydride reagents (NaBH_4 , LiAlH_4)
- Alkyl lithium reagents (RLi)
- Grignard reagents (RMgBr)

Reversible addition to aldehydes and ketones: Reactions that involve the addition of nucleophiles to the $\pi^*_{C=O}$ to form products that are of similar stability to the starting materials. Often, these reactions are catalyzed by acid or base.



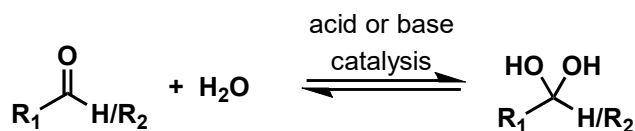
Reversible addition nucleophiles: neutral reagents with nucleophilic lone pairs, and negatively charged reagents in which the negative charge is localized on atoms that are very electronegative (usually O)

- Water
- Alcohols
- Cyanide

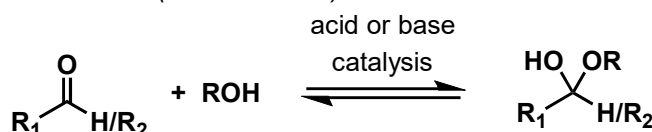
We have seen examples of the carbonyl functional group acting as an electrophile in both reversible and irreversible reactions. Some examples are listed below. You should be comfortable drawing mechanisms for all of these reactions in both the forward and reverse directions (for reversible reactions only)! (see lecture notes or Clayden Ch. 6 for review)

Reversible Carbonyl Addition Reactions

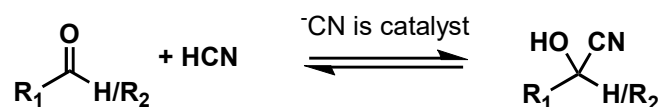
Hydrate formation



Hemiacetal (and hemiketal) formation



Cyanohydrin formation

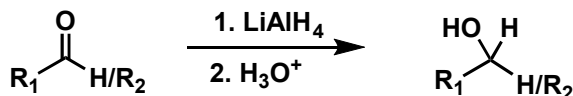
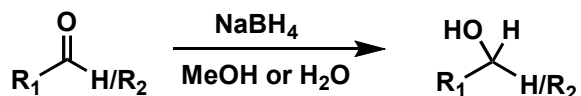


Note:

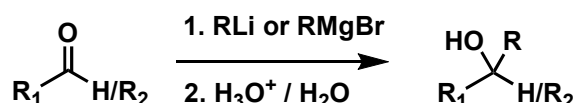
1. acid catalysts are the conjugate acid of the reactant, so H_3O^+ or ROH_2^+
2. base catalysts are the conjugate base of the reactant, so ^-OH or RO^-
3. ^-CN is the conjugate base of the reactant, HCN.

Irreversible Carbonyl Addition Reactions

Reduction of carbonyl to alcohol



Addition of a carbon nucleophile to a carbonyl



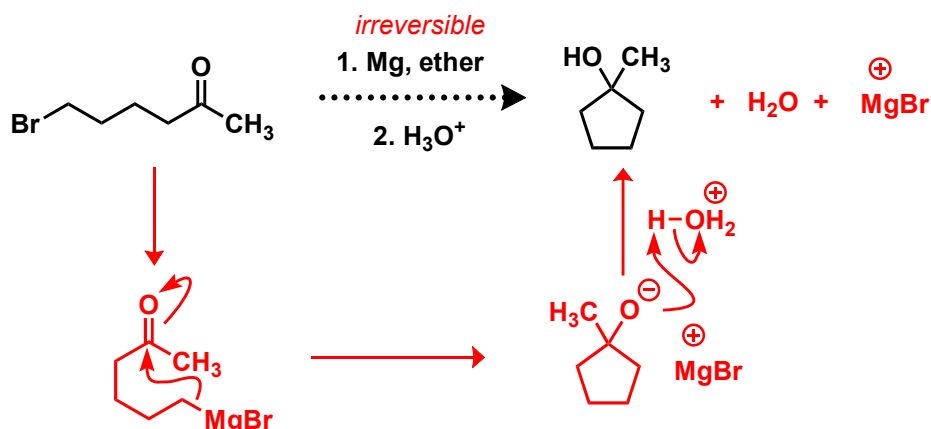
Note: We must indicate that the acid was added **after** the alkyl lithium or Grignard reagent has reacted; acid will destroy these reagents.

Workshop Problems

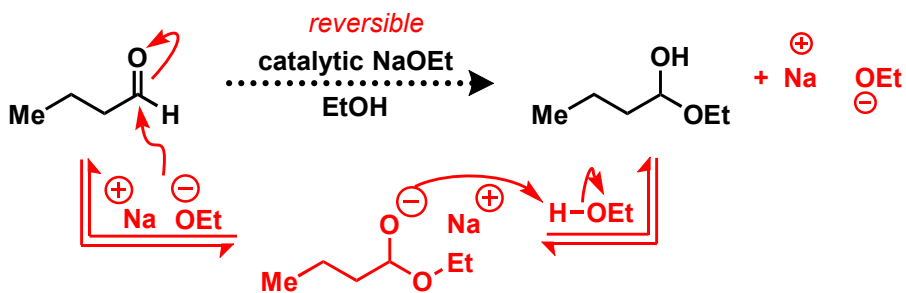
Workshop Problem 1: Mechanisms of Carbonyl Addition Reactions

Propose a mechanism for each of the following reactions, using curly arrows to depict the redistribution of electrons in each step. Indicate whether each reaction is reversible or irreversible. You do not need to provide arrows for the formation of organometallic compounds. The dotted arrows are intended to show the reaction under consideration, and the direction in which it is being considered. The arrow does not specify if the reaction actually occurs or not, or if it is reversible.

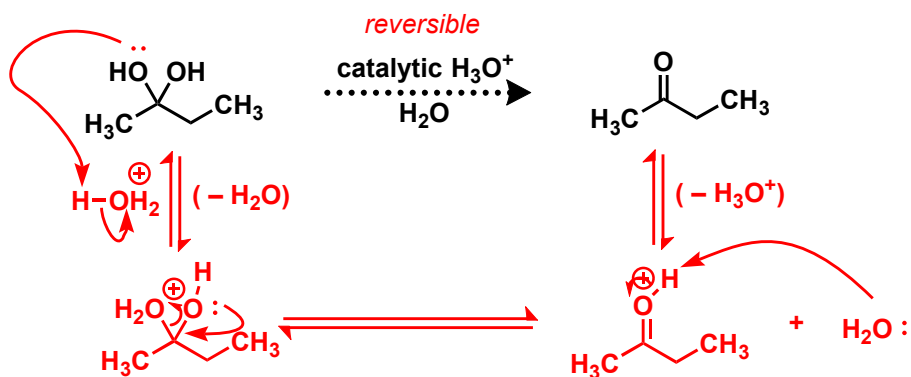
1-a.



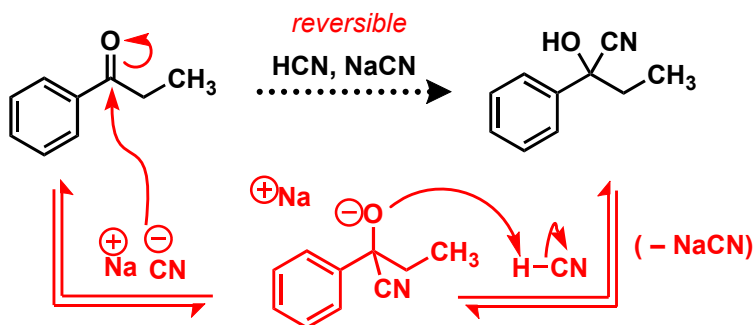
1-b.



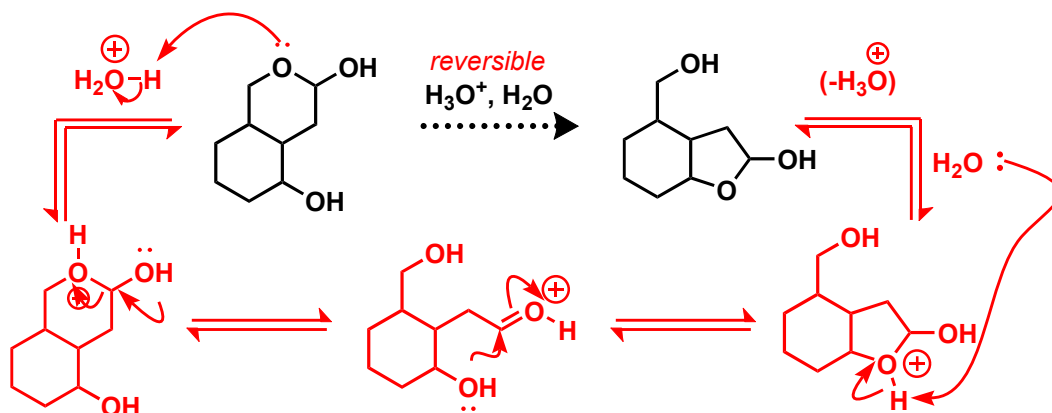
1-c.



1-d.

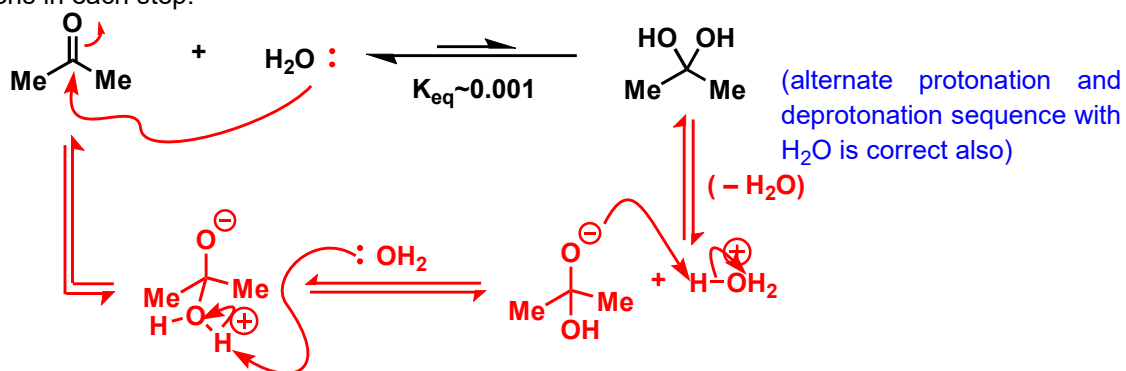


1-e.

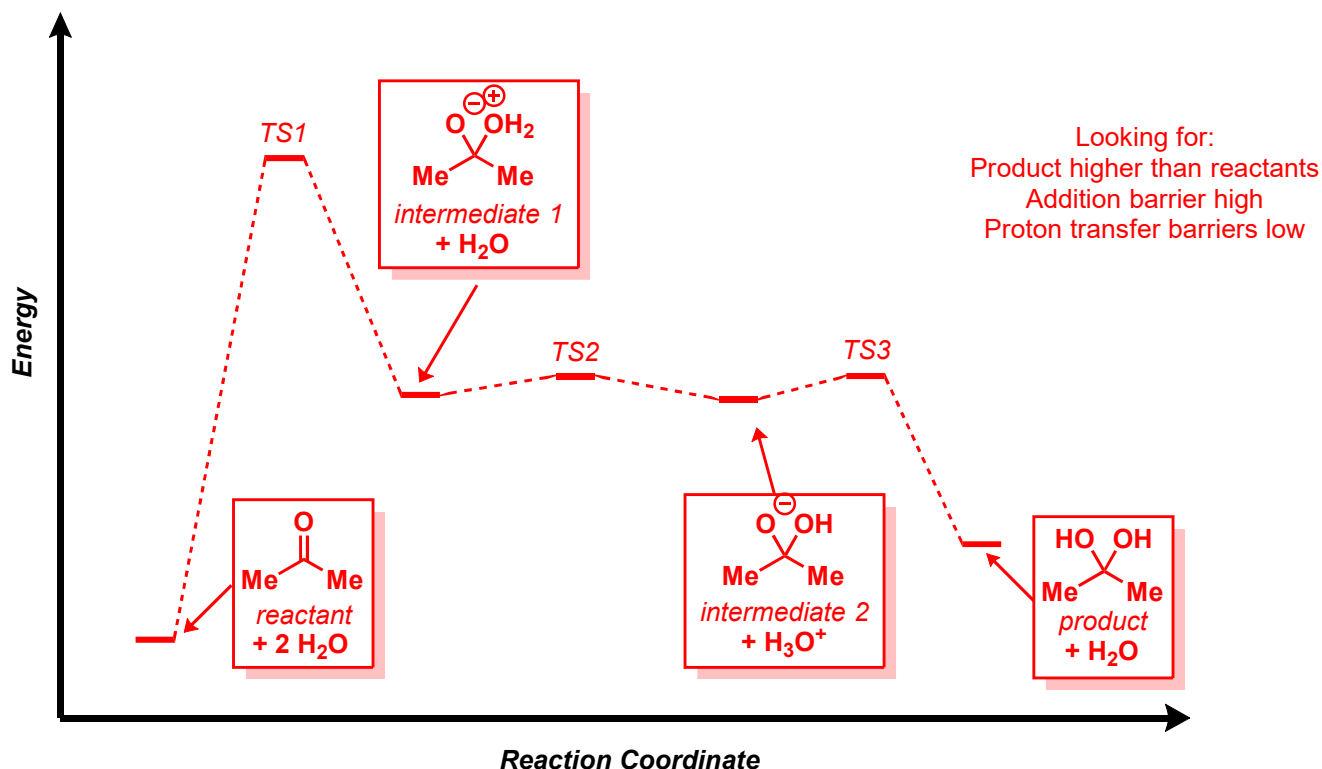


Workshop Problem 2: Reaction Energy Profile Diagrams

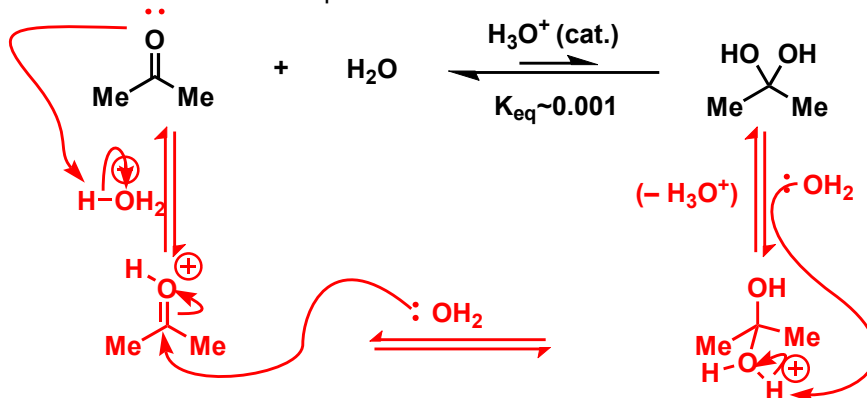
2-a. Propose a mechanism for the ketone hydration shown below, using the arrow pushing formalism to depict the redistribution of electrons in each step.



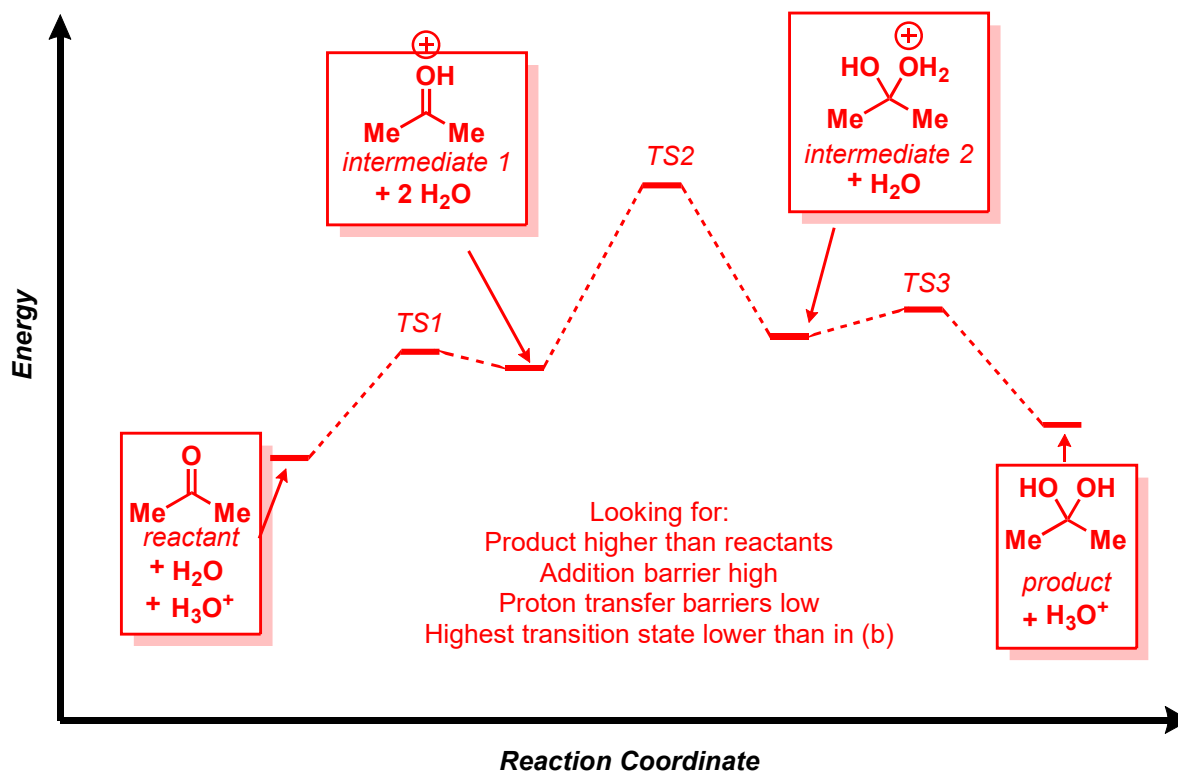
2-b. Draw a reaction energy profile diagram for the ketone hydration (from part **a**) on the axes below. Include and label ALL reactants, intermediates, transition states, and products, and clearly place them at the correct relative energy levels.



2-c. Propose a mechanism for the acid-catalyzed ketone hydration shown below, using the arrow pushing formalism to depict the redistribution of electrons in each step.



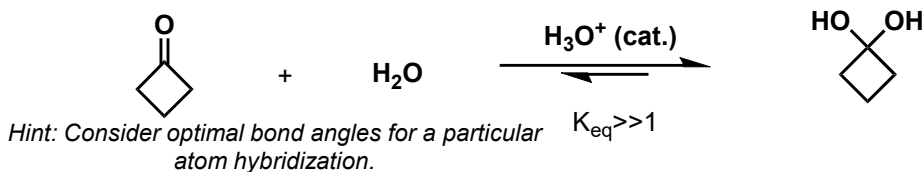
2-d. Draw a reaction energy profile diagram for the acid-catalyzed ketone hydration (from part c) on the axes below. Include and label ALL reactants, intermediates and products, and clearly place them at the correct relative energy levels.



2-e. Predict whether the reaction in part a or part c will proceed more rapidly and provide an explanation for your answer based on your energy diagrams.

The reaction proceeds faster in the presence of an acid because the acid-catalyzed reaction path has a lower energy barrier (activation energy, or E_a) than the non-catalyzed reaction path.

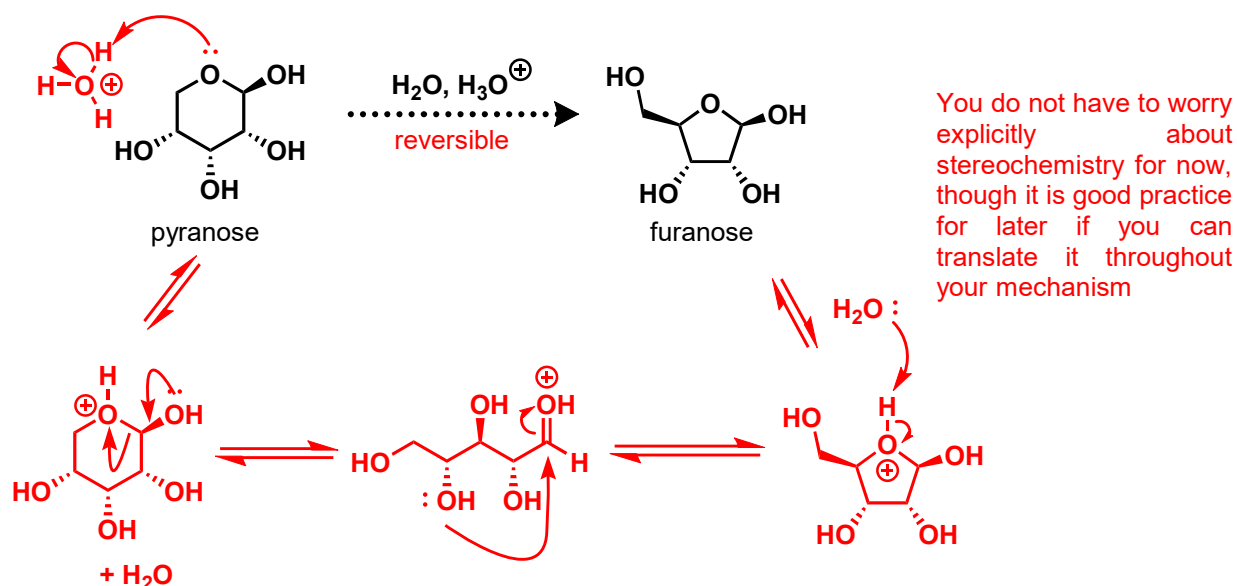
2-f. When exposed to the same reaction conditions as above, cyclobutanone has an equilibrium constant that is much greater than 1. Identify the primary source of this difference in equilibrium constants.



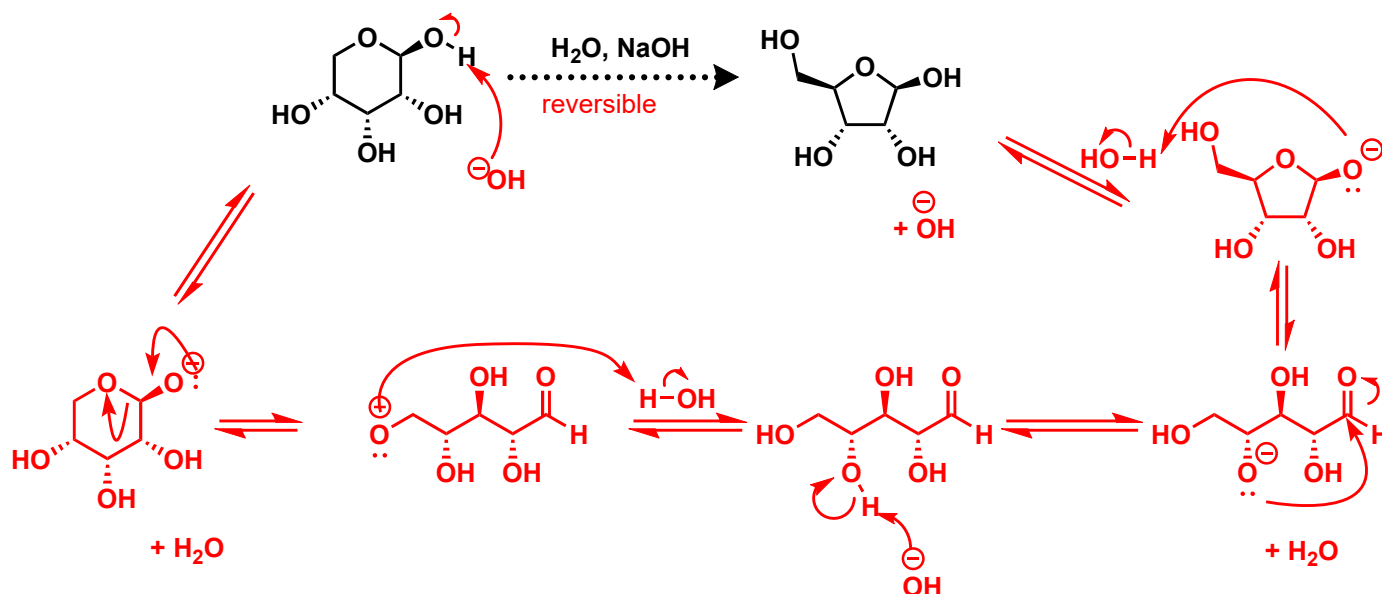
The reaction to form the hydrate relieves ring strain. Cyclobutanes have bond angles of nearly 90 degrees; the sp^2 carbon in cyclobutanone would like to achieve ideal angles of 120 degrees. This strains the ring. Because the hydration product is sp^3 hybridized at the corresponding carbon, it has ideal bond angles of 109 degrees. This product has far less strain than the starting material.

Workshop Problem 3: Ribose can exist in two different forms: pyranose (the six-membered ring) and furanose (the five membered ring). These isomers of ribose have biological significance, as some enzymes prefer one isomer over the other. Under acid or base catalysis, the isomers are in equilibrium and interconvert between the closed ring hemiacetals *via* an open chain aldehyde intermediate.

- 3-a.i) With the information above, propose a mechanism for the conversion of the pyranose form of ribose to the furanose form of ribose found in RNA using the curved arrow formalism.
 ii) Indicate whether each step is reversible or irreversible and whether the overall transformation is reversible or irreversible.



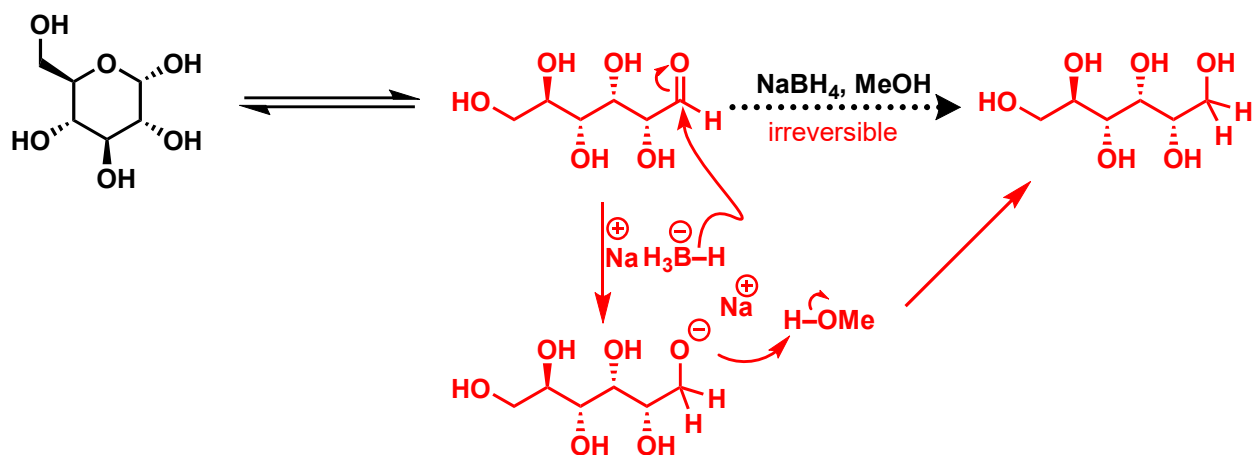
3-b. Do the same as in 3-a, except under base catalysis.



3-c. Look at the mechanisms you drew in parts 3-a,b. Do you observe any trend about the formal charges on intermediates in the acid catalyzed mechanism versus the base catalyzed mechanism? Why is this observation true, and can this trend be generalized to other acid/base catalyzed reactions?

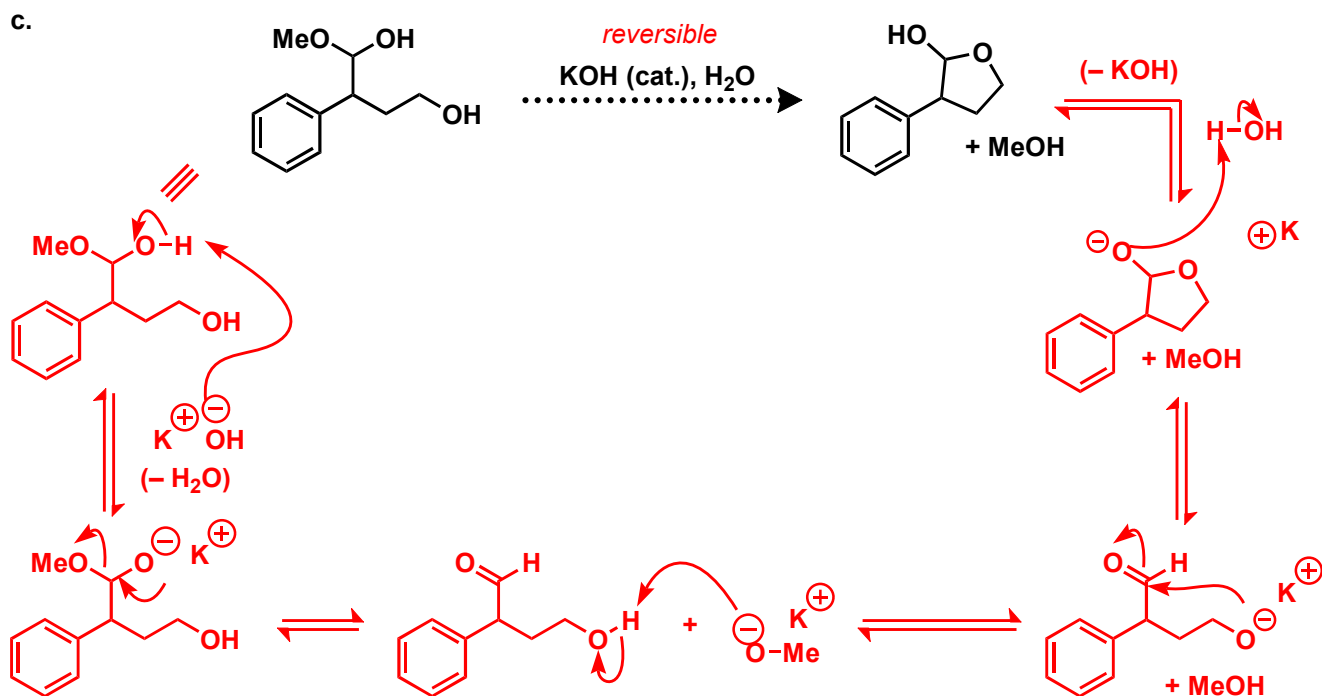
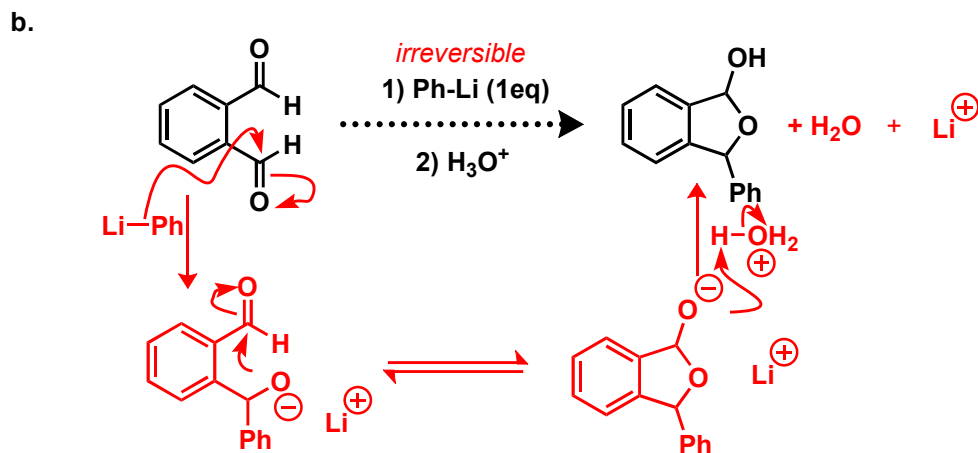
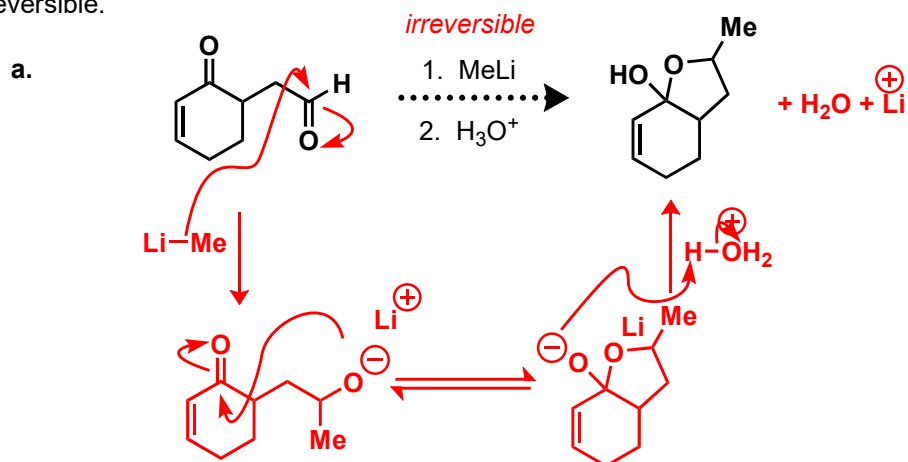
Under acid catalysis, all intermediates are cationic or neutral. In base catalysis all intermediates are anionic or neutral. In general this should be true because if we were to have negatively charged species under acidic conditions, the anionic intermediates would likely be basic and be protonated, quenching the negative charge. Similarly, if we were to have positively charged species under basic conditions, the cationic intermediates would likely be acidic and be deprotonated, quenching the positive charge.

- 3-d** The closed ring version of glucose is shown below. Commercial production of the sugar substitute sorbitol begins with opening of the ring followed by reduction with sodium borohydride.
- Draw the expected open chain of glucose given your results in 3-a. and the product of the borohydride reduction (you do not need to show the mechanism).
 - Propose a mechanism for the reduction step. Move electrons using the arrow pushing formalism.
 - Indicate whether each step is reversible or irreversible and whether the overall transformation is reversible or irreversible.

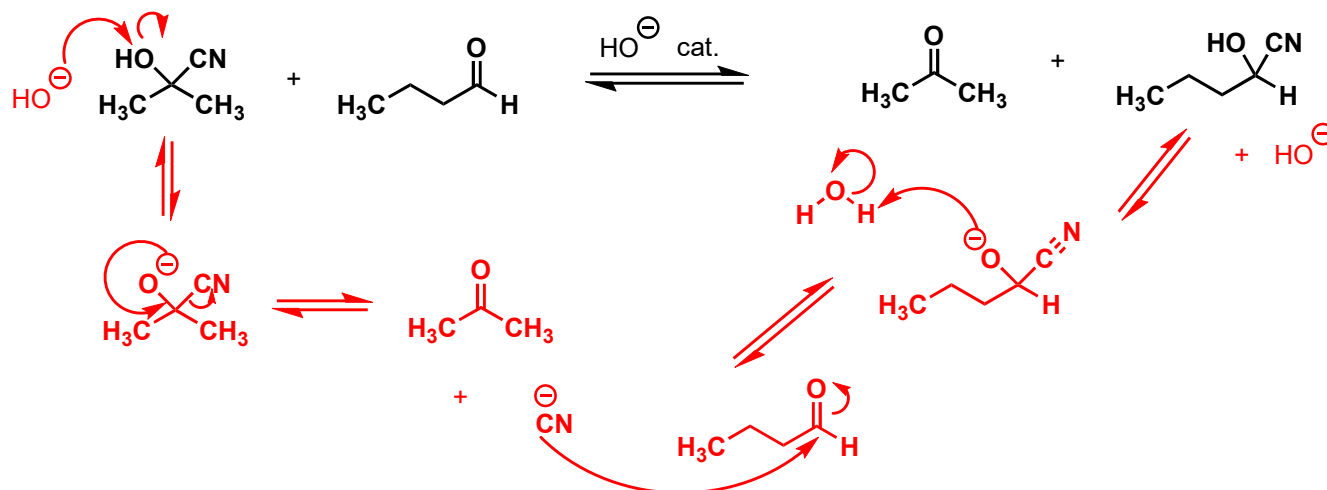


Practice Problems

1. Skillbuilder Problem 1: Mechanisms of Carbonyl Addition Reactions Propose a mechanism for the each of the following reactions, using curly arrows to depict the redistribution of electrons in each step. Indicate whether each reaction is reversible or irreversible. You do not need to provide arrows for the formation of organometallic compounds. The dotted arrows are intended to show the reaction under consideration, and the direction in which it is being considered. The arrow does not specify if the reaction actually occurs or not, or if it is reversible.



2-a. Skillbuilder Problem 2 Propose a mechanism for the following reaction, using curly arrows to depict the redistribution of electrons in each step. Indicate whether each step is reversible or irreversible.



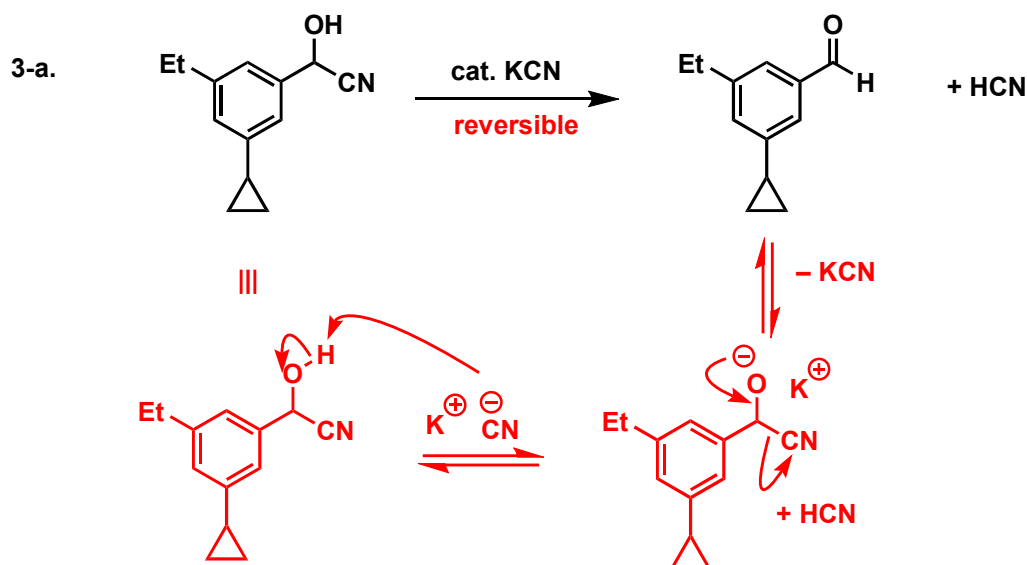
2-b. $K \gg 1$ for the reaction in part a. Propose an explanation.

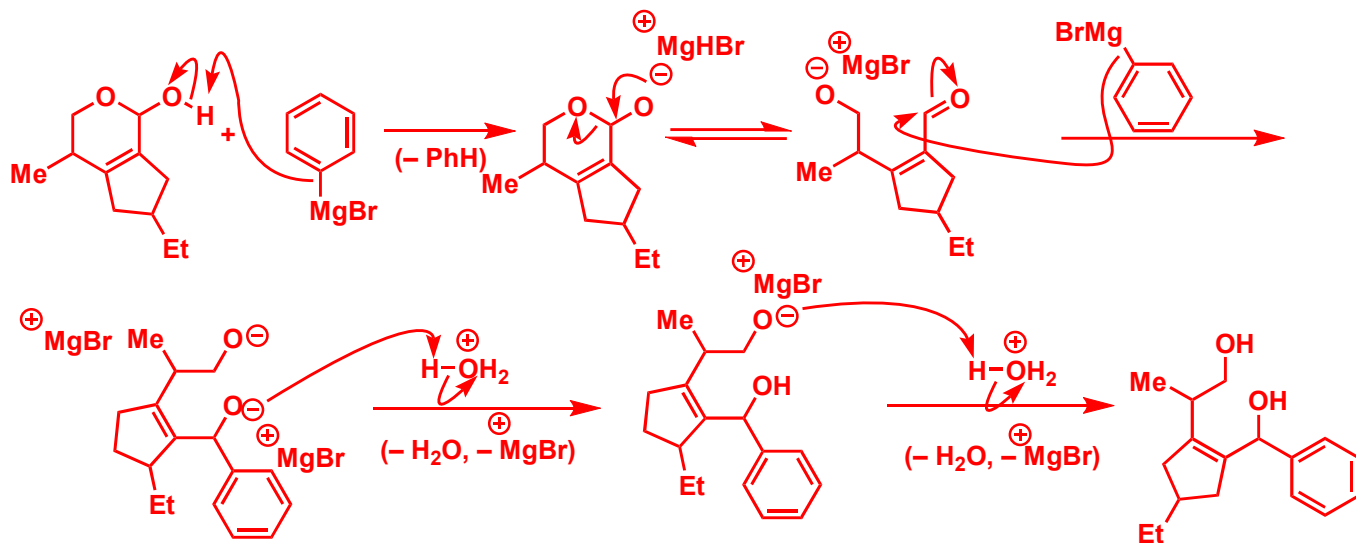
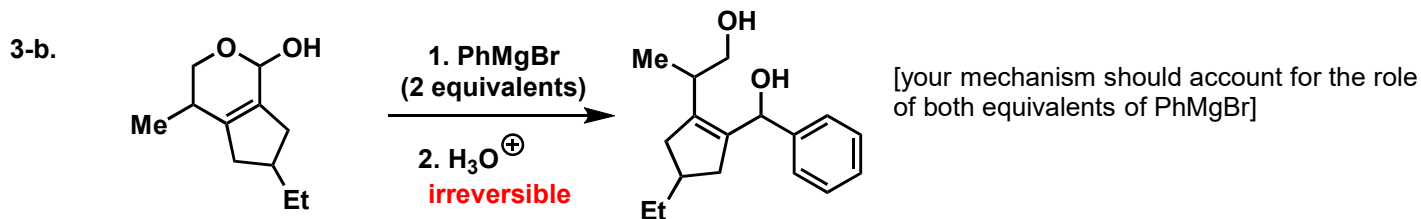
The product cyanohydrin is derived from an aldehyde, whereas the starting cyanohydrin is derived from a ketone. The addition product of the aldehyde is more stable than that of the ketone, because of steric factors. The decrease in bond angle going from $\text{sp}^2\text{-C}$ in the carbonyl compound to $\text{sp}^3\text{-C}$ in the cyanohydrin is more favorable for the aldehyde which has an H, the smallest possible substituent, at this position. Acetone cyanohydrin can be used as a more benign source of highly toxic HCN because of the reversibility of cyanohydrin formation.

Skillbuilder Problem 3

i) Propose mechanisms for each of the following reactions. Depict the motion of electrons using the arrow pushing formalism.

ii) Indicate whether each step is reversible or irreversible and whether the overall transformation is reversible or irreversible.

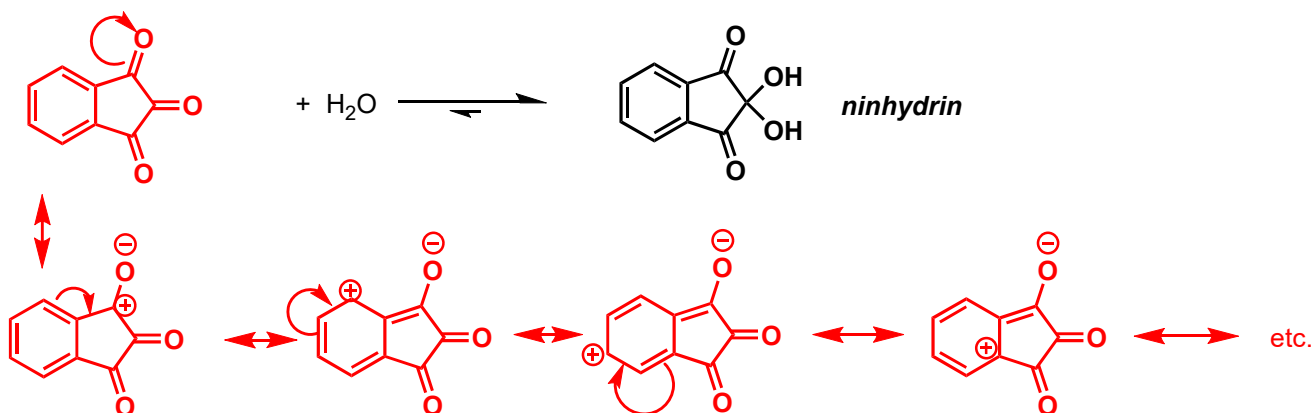




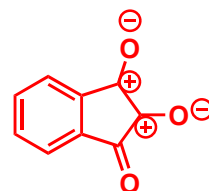
(The protonations of the two alkoxides can occur in either order)

Challenge Problem 1 The molecule, ninhydrin, shown below is widely used as a sensitive test for the presence of certain amino acids. Spraying surfaces with a solution of ninhydrin reveals latent fingerprints by staining them purple. Amino acids in the protein and peptide residues left by the finger on the surface react with the ninhydrin to produce a highly colored compound.

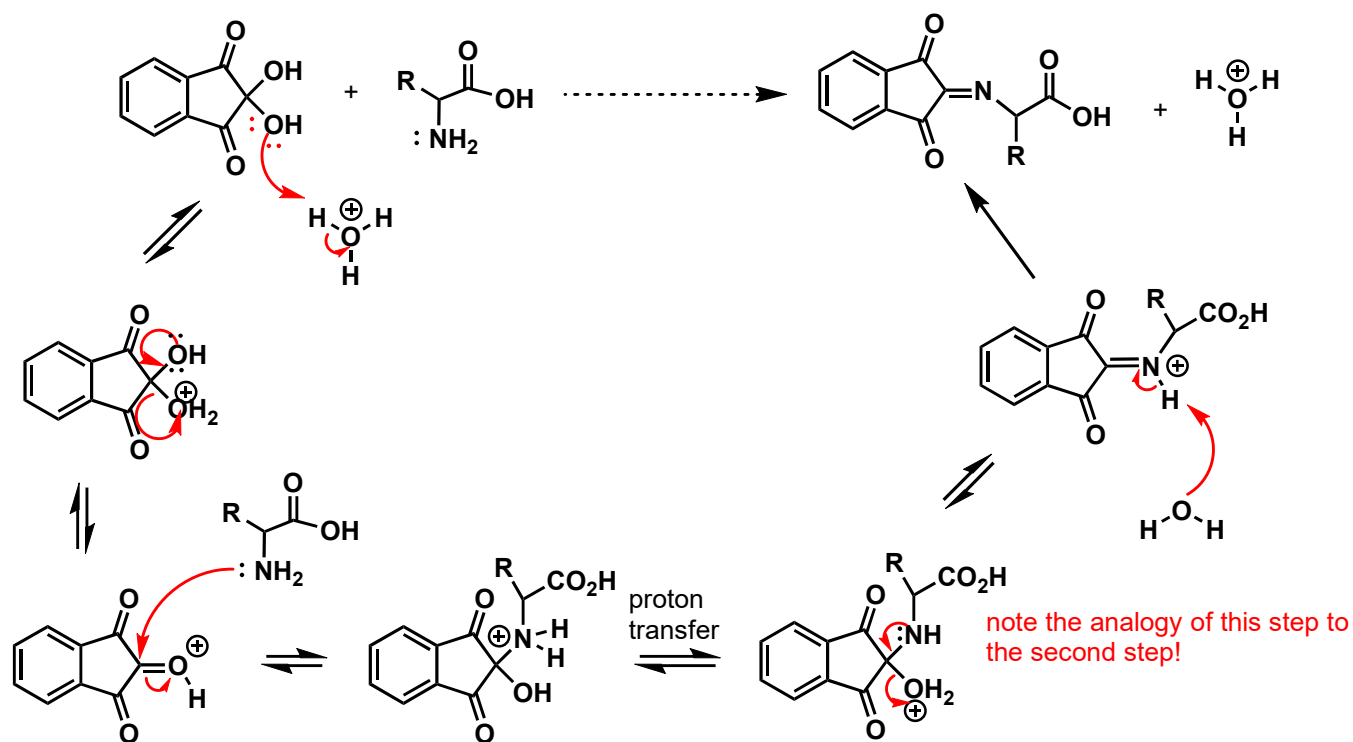
1-a. Ninhydrin is an unusual example of a highly stable solid hydrate, i.e K for the reaction to form the hydrate from the carbonyl is $\gg 1$. Draw the carbonyl compound from which ninhydrin is derived. Explain why the central carbonyl group is the most reactive carbonyl group in this molecule.



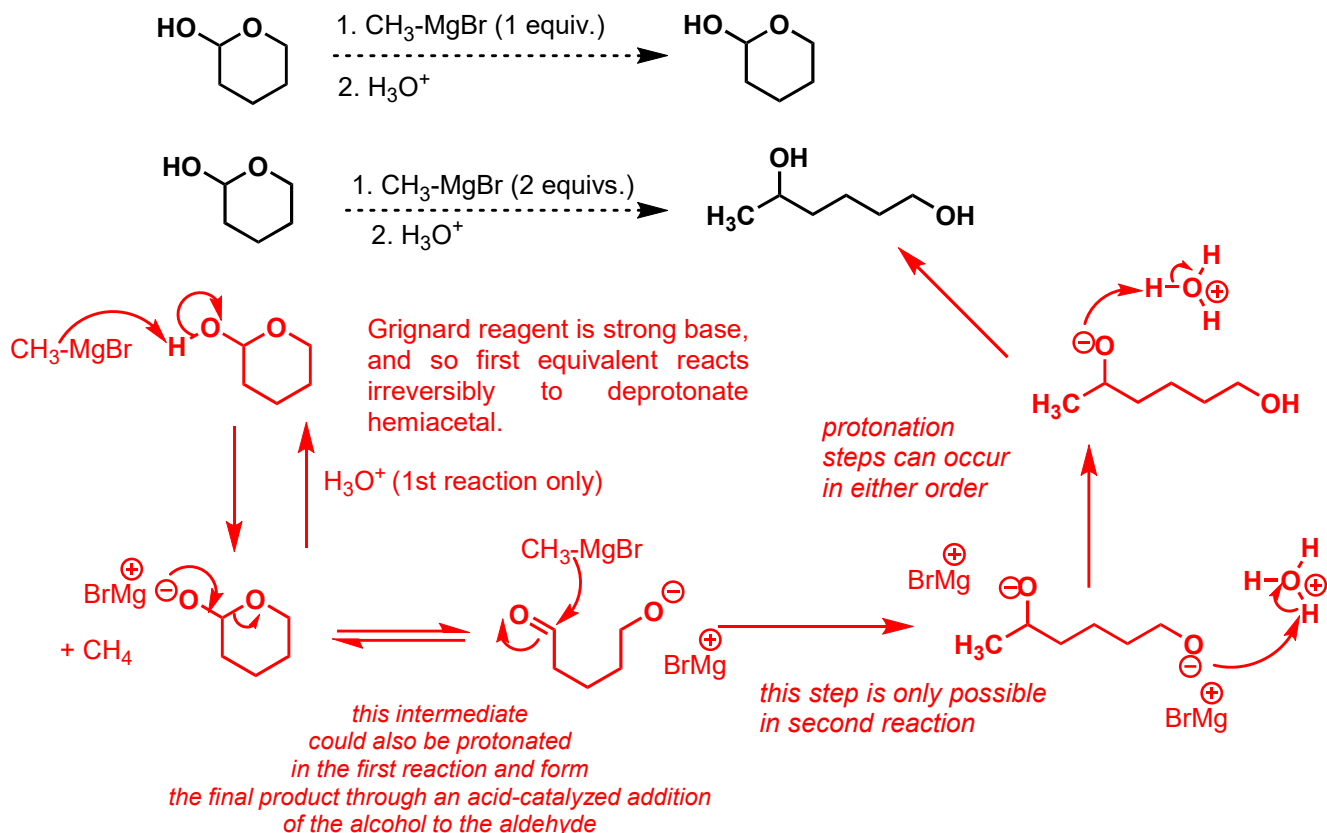
The reactivity of the central carbonyl can be rationalized in several ways. First by consideration of the resonance shown above which indicates that the carbonyl groups directly attached to the arene are stabilized by resonance whereas the central carbonyl is not. Notice also that there are partial positive charges on the three adjacent C atoms of the 3 carbonyl groups which is destabilizing, and can be thought of in terms of resonance structures such as that shown to the right. In addition, the carbonyl compound has a 5 membered ring containing 5 sp²-C atoms: Conversion of one C atom to an sp³-C with a smaller bond angle relieves significant ring strain.



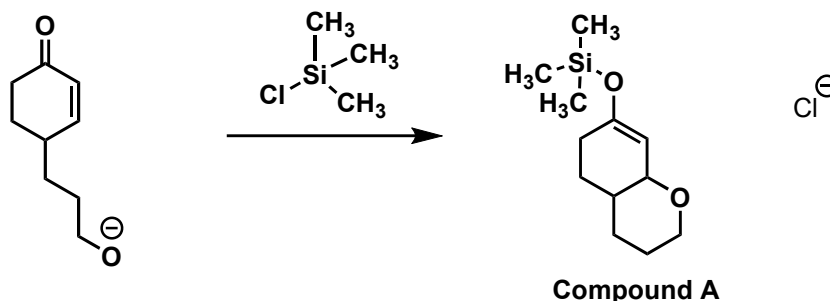
1-b. Analogous chemistry to hydration/hemiacetal formation can occur with amines, and is part of the pathway of the reaction of ninhydrin with an amino acids, which ultimately forms the purple product (structure not shown). Add arrow-pushing to the intermediates below to complete the mechanism.



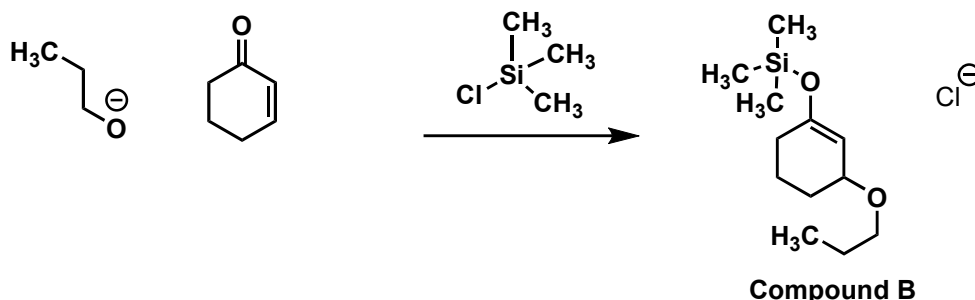
Challenge Problem 2: Explain the outcome of these 2 reactions by drawing a mechanism for each. Indicate whether each step is reversible or irreversible.



Challenge Problem 3: A new graduate student to Harvard University Chemistry Department wanted to make **Compound A** using the reaction shown below.



When this graduate student attempted a similar reaction to make **Compound B**, they found that this reaction did not work at elevated temperature (80°C) and only proceeded at lower temperature (-20°C).



When the graduate student varied the temperature of the reaction to make **Compound A**, the student did not observe any variation in the reaction's ability to proceed forward to the product. Please provide a rationale for this observation. (You do not need to draw any mechanisms to answer this question.)

We can rationalize this observation by studying the differences in the Gibbs free energy equation for each of these reactions. The Gibbs free energy equation is as follows:

$$\Delta G = \Delta H - T\Delta S$$

Since both reactions occur, albeit at different temperatures, we know that the sign of ΔG must be negative. We can also say that the sign of the entropy term is negative since both reactions have products that are less 'random' than the starting material. The reaction to form **Compound B** should have an entropy term with a larger magnitude because it has 3 reactants that yield 2 products whereas the reaction to form **Compound A** has 2 reactants that yield 2 products. Because the reaction to form **Compound B** has an entropy term that is large and negative, if we increase the temperature of the reaction too much, this value will overshadow the ΔH term and result in a ΔG that is positive and thus a reaction that does not proceed. Since the reaction to form **Compound A** has an entropy term that is small and negative, it is less sensitive to variations in temperature.

Note: we expect the ΔH term to be very similar in each case as the same bonds are formed and broken in each reaction.